REMARKS

Status of the Claims

Claims 1-2, 6-10, 16-33, and 39 are pending. Claims 1, 2, 16, 37, and 38 are amended. Claim 39 is newly added. Claims 9-11 are canceled without prejudice or disclaimer to the subject matter therein. Support for the amended and new claims can be found throughout the specification and in the claims as originally filed. *See, e.g.*, Specification, paragraphs [020], [025], and [043].[1]

Withdrawn Rejection

Applicants appreciate the Examiner's withdrawal of the new matter rejection.[2]

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4, 6, 16-33, 37, and 38 stand rejected under 35 U.S.C. § 112, 1st paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* and *in vivo* comprising introducing nucleotide sequences coding for a nuclear localization signal, D-type cyclin gene (D1, D2, or D3) and a cyclin dependent kinase gene (CDK4 or CDK6) directly into the cardiomyocytes using an adenoviral expression vector, allegedly does not reasonably provide enablement for a method of proliferating cardiomyocytes using any vector for introducing the required nucleotide sequences.[3]

Applicants respectfully traverse.

A. The Office Action Fails To Establish A *Prima Facie* Enablement Rejection

The Office Action contends that "any vector or any viral vector would not predictably provide sufficient directed delivery and expression of the cyclin and CDK genes, absent further undue experimentation."[4]

Applicants respectfully disagree and submit that the Office Action fails to establish a *prima facie* case of enablement. Indeed, the Office Action does not provide any evidence for the above-

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[1] Applicants appreciate the Examiner's entry of Applicants' January 9, 2009 amendments.

[2] *See* Advisory Action, page 2.

[3] *See* Office Action, page 4; *see also* Advisory Action, page 2.

[4] Office Action, page 5; *see also* Advisory Action, page 2.

quoted assertion.[5] Rather, the evidence of record and that presented herein demonstrates that vectors (e.g., viral and liposomal vectors) were well known and used in the art, at the time of filing, for successfully delivery of genes into cardiomyocytes. As is well established, the bare assertion of unpredictability is legally insufficient to make out a *prima facie* case of non-enablement.[6] Accordingly, for at least this reason, Applicants request that the rejection be withdrawn.

B. The Full Scope Of The Claimed Invention Is Enabled

The claims are directed to methods of proliferating cardiomyocytes comprising administering various nucleic acids directly into cardiomyocytes using a vector.

The evidence of record and that presented herein demonstrates that the use of vectors in the claimed invention is enabled. First, as the Office Action acknowledges, the specification teaches the use of an adenoviral vector.[7] Second, the specification discloses the use of vectors other than adenoviral vectors (e.g., viral vectors).[8] Third, the specification teaches that a nuclear localization signal is added to direct delivery and expression of the cyclin and CDK genes.[9] Fourth, the state of art establishes that the use of vectors (including non-adenoviral vectors) is enabled. Indeed, in its prior response, Applicants identified numerous U.S. patents directed to cardiovascular-related methods comprising administering ***any*** vector comprising a nucleic acid to an individual (e.g., human).[10]

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[5] The Office Action previously cited Tamamori-Adachi et al. and Nicol et al. to support an assertion that the art is unpredictable, but this assertion did not in any way relate to vectors. Applicants addressed these references in its prior response. *See* Applicants' response, filed April 4, 2008, pages 8 and 9.

[6] *See Ex Parte Goeddel*, 5 USPQ 2d 1449, 1450 (PTO Bd App. & Int. 1987) ("Mere broad generalizations and allegations are insufficient for holding of non-enablement.")

[7] *See, e.g.*, Specification, Example 5; *see also* Office Action, page 5 ("...the instant specification exemplifies the delivery of the cyclin and CDK genes via an adenoviral expression vector...").

[8] *See, e.g.*, Specification, ¶¶ [045]-[046], and [048]; *see also* Office Action, page 2 ("...the specification discloses several modes of gene delivery (microinjection, liposome, calcium phosphate transfection and viral)...).

[9] *See, e.g.*, Specification, ¶ [043].

[10] *See* Applicants' response, filed January 9, 2009, pages 8-9. Several of these patents disclose a single or no working examples of using a vector. For example, U.S. Patent No. 6,224,584, does not teach a single example of introducing a gene into a heart, but claims various gene therapy methods using any vector. Likewise, U.S. Patent No. 5,797,870, purports to disclose an example of

In the Advisory Action, the Examiner asserts that each patent application is examined on its on merits.[11] Applicants appreciate the Examiner's comment, but point out that the cited patents are evidence of at least the state of the art—a *Wands* factor. These patents demonstrate that the use of vectors (including non-adenoviral vectors) were well known at the time of filing the instant application.

In further support of Applicants' arguments, Applicants attach herewith a Declaration Under 37 C.F.R. § 1.132 of Uichi Koshimizu, Ph.D.[12]

In his declaration, Dr. Koshimizu states that "numerous methods of stably and efficiently transferring cardiomyocytes with foreign DNA were well known in the art at the time the '008 application was filed."[13] Dr. Koshimizu discusses "literature that was widely available and that persons skilled in the art during the time the '008 application would no doubt have been familiar with."[14] In particular, Dr. Koshimizu identifies fourteen pre-filing date references that demonstrate methods such as direct injection of plasmid DNA, gene-gun mediated transfer of plasmids and viral-based vectors, liposomal transfer of vector DNA, transfection with adeno-associated vector DNA, and transduction with retroviral-based vectors were well known methods for stably and efficiently introducing foreign genes into cardiomyocytes.[15] Dr. Koshimizu concludes that "these references directly refute the Examiner's contention that, prior to May 2001, non-adenoviral and retroviral vectors were incapable of stably and efficiently transforming cardiomyocytes with foreign DNA."[16]

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using an adenovirus vector, but claims methods of treating a patient's heart using any vector such as viral and retroviral vectors.

[11] *See* Advisory Action, page 2.

[12] Dr. Kohimizu is the manager and chief researcher at Asubio Pharma. Co., Ltd., the exclusive licensee of the above-identified application. This is Dr. Koshimizu's second Declaration. *See* Response filed July 6, 2007. Applicants note that Dr. Koshimizu's Declaration does not contain an Exhibit B.

[13] Declaration Under 37 C.F.R. § 1.132 of Uichi Koshimizu, Ph.D. ("Koshimizu Dec."), ¶ 12.

[14] *Id.*

[15] *Id.* at ¶¶ 13-26.

[16] *Id.* at ¶ 26.

In view of the foregoing, Applicants submit that the full scope of the claimed invention is enabled. Accordingly, Applicants respectfully request withdrawal of this rejection.

C. Claims 6 and 39

Claims 6 and 39 are directed to the methods of claims 2 and 1, respectively, where the recited genes are transferred into cardiomyocytes via an adenovirus vector. The USPTO indicates that such methods are enabled.[17] Accordingly, Applicants respectfully request an indication that at least claims 6 and 39 are allowable.

CONCLUSION

It is believed that these amendments and remarks should place this application in condition for allowance. A notice to that effect is respectfully solicited. If the Examiner has any questions relating to this response or the application in general he is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

HUNTON & WILLIAMS, LLP

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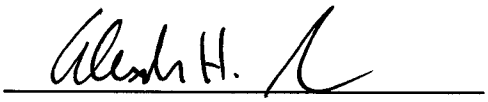
By: 

Robert M. Schulman
Registration No. 31,196

Alexander H. Spiegler
Registration No. 56,625

HUNTON & WILLIAMS, LLP
Intellectual Property Department
1900 K Street, N.W., Suite 1200
Washington, D.C. 20006–1109
(202) 955-1500 (telephone)
(202) 778-2201 (facsimile)

[17] *See* Office Action, page 4; *see also* Advisory Action, page 2.